APPendix A

Claim Rejections under 35 U.S.C. §112, first paragraph

Claims 27-38, 45 and 51 were rejected under 35 U.S.C. §112, first paragraph for enablement. In particular, the Examiner alleged that

> The specification is enabling only for the polypeptides of SEQ ID Nos: 2, 4, 6 and 8 as disclosed in the specification. The specification states that "variant refers to a polynucleotide or polypeptide that differs from a reference polynucleotide or polypeptide but retains essential properties" and "generally differences are limited that the sequences of the reference polypeptide and the variant are closely similar overall and in many regions are identical." The specification states "that a variant and reference polypeptide may differ in amino acid sequence by one or more substitutions, additions, deletions in any combination" and "that a substituted or inserted amino acid residue may or may not be encoded by the genetic code" (page 48). There is no guidance provided as to which amino acids can be added, deleted or substituted and still have the polypeptide retain its biological function. The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of polypeptides broadly encompassed by the claims and the claims broadly encompass a significant number of inoperative species. Since the amino acid sequence of the polypeptide determines its structural and functional properties, predictability of which changes can be tolerated in a polypeptide's amino acid sequence and still retain similar activity requires a knowledge with regard to which amino acids in the polypeptide's sequence, if any, are tolerant of modification and which are conserved (i.e., expected intolerant to modification) and detailed knowledge of the ways in which the polypeptide's structure relates to function. However, the problem of the prediction of polypeptide structure from mere sequence data of a single polypeptide and in turn utilizing predicted structural determinations to ascertain functional aspects of the polypeptide and finally what changes can be tolerated with respect to thereto is extremely complex and outside of the realm of routine experimentation.
>
> While recombinant and mutagenesis techniques are known, it is not routine in the art to screen multiple substitutions or multiple modifications of other types and the positions within the polypeptide's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining similar activity are limited in any polypeptide and the result of such modifications is unpredictable based on the instant disclosure. One skilled in the art would expect any tolerance to modifications, e.g., multiple substitutions. The sequence of some polypeptides is

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highly conserved and one skilled in the art would not expect tolerance to any amino acid modification in such polypeptides.

The claims of the instant application are not only drawn to isolated immunogenic polypeptides but are also drawn to isolated immunogenic polypeptides, which comprise at least 15 amino acids. There is no guidance provided in the specification as how one would begin to choose "at least 15 amino acids". The specification does not support the broad scope of the claims, which encompass all modifications and fragments because the specification does not disclose the following:

- the general tolerance to modification and extent of such tolerance;
- specific positions and regions of sequence(s) which can be predictably modified and which regions are critical;
- which fragments, if any, can be made which the retain the biological activity if the intact protein; and
- the specification provide essentially no guidance as to which of the essentially infinite possible choice is likely to be successful.

Factors to be considered in determining whether undue experimentation is required, are set forth in In re Wands 8 USPQ2d 1400. The include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art and (8) the breadth of the claims.

Applying the above test to the facts of record, it is determined that 1) no declaration under 37 C.F.R. 1.132 or other relevant evidence has been made of record establishing the amount of experimentation necessary, 2) insufficient direction or guidance is presented in the specification with respect to selecting other antigens having claimed functional features, 3) the relative skill of those in the art is commonly recognized as quite high (post-doctoral level). One of skill in the art would require guidance, in order to make or use polypeptides that are variants of SEQ ID NO:2, 4, 6 and 8 in a manner reasonable in correlation with the scope of the claims. Without proper guidance, the experimentation to is undue.

The Applicant has not provided sufficient guidance to enable one of skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including any number of additions, deletions or substitutions and fragments of any size. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970). Without such

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> guidance the changes which can be made in the protein's structure and still maintain activity is unpredictable and the experimentation left those skilled in the art is unnecessary and improperly, extensive and undue. See Amgen Inc. v. Chugai Pharmaceutical Co Ltd. 927 F 2d 1200, 18 USPQ2d 1016 (Fed. Cir. 1991) at 18 USPQ2d 1026-1027 and Ex parte Forman, 230 USPQ 46 (Bd Pat App. & Int. 1986).

Without conceding any aspect of the rejection, Applicants have elected to present the invention in different terms, which terms obviate the present rejection. Reconsideration and withdrawal of this rejection is respectfully requested.

Claims 52-53 were rejected under 35 U.S.C. §112, first paragraph for enablement. In particular, the Examiner alleged that

> [c]laims 52-53 are drawn to a vaccine comprising the polypeptide of claim 27 and a pharmaceutically acceptable carrier.
>
> The specification fails to teach how to use the claimed vaccines for protection. The term "vaccine" encompasses the ability of the specific antigen to induce protective immunity to a bacterial infection or disease induction. The specification states that "the dosage range required depends on the choice of peptide, the route of administration, the nature of the formulation, the nature of the patient's condition and the judgment of the attending practitioner" (page 40). The specification further teaches that rabbits were vaccinated intramuscularly with the purified recombinant BASB034 protein and the animals produced high antibody titers (pages 62-63, Example 5 and Figure 6).
>
> The specification does not provide substantive evidence that the claimed vaccines are capable of inducing protective immunity. This demonstration is required for the skilled artisan to be able to use the claimed vaccines for their intended purpose of treating bacterial infections. Without this demonstration, the skilled artisan would not be able to reasonably predict the outcome of the administration of the claimed vaccines, i.e. would not be able to accurately predict if protective immunity has been induced. The ability to reasonably predict the capacity of a single bacterial immunogen or combinations of immunogens to induce protective immunity from *in vitro* antibody reactivity studies is problematic. Ellis (*Vaccines, W.B. Saunders Company*, 1988, Chapter 29) exemplifies this problem in the recitation that "the key to the problem (of vaccine development) is the identification of a protein component of a virus or microbial pathogen that itself can elicit the production of protective antibodies" (page 572, second full paragraph). Unfortunately, the art is replete with instances where even well characterized antigens that induce an *in vitro*

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neutralizing antibody response fail to elicit *in vivo* protective immunity. Boslego et al (Vaccines and Immunotherapy, Pergaman Press, 1991, Chapter 17) teach a single gonococcal pillin protein wherein the protein fails to elicit protective immunity even though a high level serum antibody response is induced (page 212, bottom of column 2). Accordingly, the art indicates that it would require undue experimentation to formulate and use a successful vaccine without the prior demonstration of vaccine efficacy.

It is well known in the art that there are several different antigens from *Moraxella catarrhalis* (i.e. outer membrane proteins, lipooligosaccharides). It is also taught that since infections caused by *Moraxella* predominately occur on mucosal surfaces, the mucosal immune response is likely important as the first line of defense. Mucosal or surface antigen immune response would likely be important in the search for candidate vaccines (Kyd et al. 2000). It has also been recognized in the art that there is currently no vaccine to prevent *Moraxellla catarrhalis* infections because of a lack of good animal models for the diseases, a lack of information about the protective antigens, a lack of *in vitro* correlates to immunity against *Moraxellla catarrhalis* in humans and the pathogenic mechanisms and host immune response to the pathogens has yet to be clarified (Chen et al. 1996; Gu et al, 1998, Hu et al. 2000; Samukawa et al 2000 and Kyd et al 2000). While studies have been shown that the outer membrane proteins can elicit bacterial antibodies, which promote bacterial clearance, the results have not lead to a predictable vaccine again infections caused by *Moraxellla catarrhalis*. A similar situation exists with the development of lipooligosaccharides (LOS) based vaccines against infections caused by *Moraxellla catarrhalis*. Clearly a great amount of experimentation would be necessary in order to develop an efficacious vaccine against *Moraxellla catarrhalis* infections.

Factors to be considered in determining whether undue experimentation is required, are set forth in In re Wands 8 USPQ2d 1400. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence or working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art and (8) the breadth of the claims.

Applying the above test to the facts of records, it is determined that 1) no declaration under 37 C.F.R. 1.132 or other relevant evidence has been made of record establishing the amount of experimentation necessary, 2) insufficient direction or guidance is presented in the specification with respect to developing a vaccine that would achieve a desire level of success when

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> administered to a patient with a bacterial infection that is capable of treating that bacterial infection, 3) there are limited working examples which suggest the desired results of a vaccine against *Moraxellla catarrhalis*, 4) the nature of the invention involved the complex and incompletely understood area of protective immune responses against *Moraxellla catarrhalis* 5) the state of the prior art shows the lack of correlates to immunity with *Moraxellla catarrhalis*, 6) the relative skill of those in the art is commonly recognized as quite high (post - doctoral level), and the lack of predictability in the field to which the invention pertains is recognized in the art as evidenced by the cited prior art.
>
> In view of all of the above, in view of the lack of predictability in the art, it is determined that it would require undue experimentation to make and use the claimed invention.

Without conceding any aspect of the rejection, Applicants have elected to present the invention in different terms in claims 60-78, which terms obviate the present rejection. Reconsideration and withdrawal of this rejection is respectfully requested.

Claim Rejections under 35 U.S.C. §112, second paragraph

Claim 34 was rejected under 35 U.S.C. §112, second paragraph for indefiniteness in recitation of the term, "a fusion protein comprising the peptide of claim 27." Clarification was requested as to what comprises a fusion protein. Claims 35 and 37 were rejected under for indefiniteness in recitation of the phrase, "the aligned sequence." Claims 45 and 51 were rejected for indefiniteness in recitation of the phrase, "conditions sufficient."

Applicants assert that new claims 60-78 do not recite any of the language which served as the basis of these rejections. Withdrawal of rejection is respectfully requested.

Claim Rejections under 35 U.S.C. §102(b)

Claims 27-32, 34-38 and 52 were rejected under 35 U.S.C. §102(b) as being anticipated by Sarwar et al. In particular, the Examiner alleged

> Sarwar et al. teach an outer membrane protein of *Moxarella catarrhalis* (formerly *Branhamella catarrhalis*) tha has a mass of 55 kDa at room temperature and 60 kDa when heated under reducing conditions. Sarwar et al teach that the expression of epitopes is independent of growth phase and growth media and are highly specific for *Moxarella catarrhalis* (see the Abstract). Sarwar et al teach epitopes of the outer membrane protein of

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> *Moxarella catarrhalis* (formerly *Branhamella catarrhalis*) that are recognized by two different antibodies, 5E8 and 7D6. Sarwar et al teach that the expression of epitopes is independent of growth phase or growht media (see the Abstract). Sarwar et al teach that the 5E8 epitope is expressed on the surface of the bacterium. Sarwar et al teach tat the epitopes are highly specific for *Moxarella catarrhalis*, being absent from a variety of other gram-negative bacteria (page 808, 2nd column). Sarwar et al teach that antibody 5E8 was produced by immunizing BALB/c mice subcutaneously with Zwittergent-extracted outer membrane of *Moxarella catarrhalis* in both complete and incomplete Freund's adjuvant (page 804, 2nd column). Sarwar et al suggest that the outer membrane of *Moxarella catarrhalis* may have a potential role as a vaccine antigen. The protein of the prior art is similar if not the same as for example, an amino acid sequence which has at least 90% identity to the SEQ ID NO:2 since they are both outer membrane proteins which have a molecular weight of about 60 kDa. The sequence of the outer membrane protein of *Moxarella catarrhalis* would be inherent in the teachings of the prior art.
>
> Since the Office does not have the facilities for examining and comparing applicant's polypeptide with the polypeptide of the prior art, the burden is on the applicant to show a novel or unobvious difference between the claimed product and the product of the prior art.

Applicants disagree. A claim is anticipated by a reference only if each and every element of the claim is found, either expressly or inherently, in that reference. *See* MPEP 2131. Moreover, the identical invention must be shown in as complete detail as is contained in the claim. *See id.* Abiding by these standards, Sarwar et al. does not anticipate the invention as presently claimed.

Sarwar et al. discloses a protein which is completely unrelated to that of the instant invention. A copy of a BLASTP sequence alignment between the Sarwar et al. protein and the instant SEQ ID NO:2 is included with this Response as Appendix **B**. Sarwar et al only discloses a protein that has a mass of 55-60 kDa and that is purported to be located on the outer membrane of *Moxarella catarrhalis*. Outer membranes of bacterium are composed of hundreds to thousands of various different proteins. Mere disclosure of an outer membrane protein having a mass in a particular range does not anticipate an unrelated protein or its amino acid sequence. Further, the Examiner's statement that "the protein of the prior art is similar if not the same as for example, an amino acid sequence which has at least 90% identity to SEQ ID NO:2" is

APPENDIX A1: PENDING CLAIMS (CLEAN COPY)

Claims following entry of amendment mailed August 16, 2002

Sub. D'

60. An isolated polypeptide comprising a member selected from the group consisting of

(a) an amino acid sequence comprising one of SEQ ID NOs:2, 4, 6 or 8; and

(b) an immunogenic fragment of at least 15 amino acids that matches an aligned contiguous segment of SEQ ID NOs:2, 4, 6 or 8; selected from the following contiguous segments thereof (identified by first and last residue number):

1-15; 2-16; 3-17; 4-18; 5-19; 6-20; 7-21; 8-22; 9-23; 10-24;11-25; 12-26; 13-27; 14-28; 15-29; 16-30; 17-31; 18-32; 19-33; 20-34; 21-35; 22-36; 23-37; 24-38; 25-39; 26-40; 27-41; 28-42; 29-43; 30-44;31-45; 32-46; 33-47; 34-48; 35-49; 36-50; 37-51; 38-52; 39-53; 40-54; 41-55; 42-56; 43-57; 44-58; 45-59; 46-60; 47-61; 48-62; 49-63; 50-64; 51-65; 52-66; 53-67; 54-68; 55-69; 56-70; 57-71; 58-72; 59-73; 60-74; 61-75; 62-76; 63-77; 64-78; 65-79; 66-80; 67-81; 68-82; 69-83; 70-84; 71-85; 72-86; 73-87; 74-88; 75-89;76-90; 77-91; 78-92; 79-93; 80-94; 81-95; 82-96; 83-97; 84-98; 85-99; 86-100; 87-101; 88-102; 89-103; 90-104; 91-105; 92-106; 93-107; 94-108; 95-109; 96-110; 97-111; 98-112; 99-113; 100-114;101-115; 102-116; 103-117; 104-118; 105-119; 106-120; 107-121; 108-122; 109-123; 110-124;111-125; 112-126; 113-127; 114-128; 115-129; 116-130; 117-131; 118-132; 119-133; 120-134;121-135; 122-136; 123-137; 124-138; 125-139; 126-140; 127-141; 128-142; 129-143; 130-144;131-145; 132-146; 133-147; 134-148; 135-149; 136-150; 137-151; 138-152; 139-153; 140-154;141-155; 142-156; 143-157; 144-158; 145-159; 146-160; 147-161; 148-162; 149-163; 150-164;151-165; 152-166; 153-167; 154-168; 155-169; 156-170; 157-171; 158-172; 159-173; 160-174;161-175; 162-176; 163-177; 164-178; 165-179; 166-180; 167-181; 168-182; 169-183; 170-184;171-185; 172-186; 173-187; 174-188; 175-189; 176-190; 177-191; 178-192; 179-193; 180-194;181-195; 182-196; 183-197; 184-198; 185-199; 186-200; 187-201; 188-202; 189-203; 190-204;191-205; 192-206; 193-207; 194-208; 195-209; 196-210; 197-211; 198-212; 199-213; 200-214;201-215; 202-216; 203-217; 204-218; 205-219; 206-220; 207-221; 208-222; 209-223; 210-224;211-225; 212-226; 213-227; 214-228; 215-229;

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APPENDIX A1: PENDING CLAIMS (CLEAN COPY) – (continued)

Sub D1

216-230; 217-231; 218-232; 219-233; 220-234;221-235; 222-236; 223-237; 224-238; 225-239; 226-240; 227-241; 228-242; 229-243; 230-244;231-245; 232-246; 233-247; 234-248; 235-249; 236-250; 237-251; 238-252; 239-253; 240-254; 241-255; 242-256; 243-257; 244-258; 245-259; 246-260; 247-261; 248-262; 249-263; 240-264; 251-265; 252-266; 253-267; 254-268; 255-269; 256-270; 257-271; 258-272; 259-273; 260-274; 261-275; 262-276; 263-277; 264-278; 265-279; 266-280; 267-281; 268-282; 269-283; 270-284; 271-285; 272-286; 273-287; 274-288; 275-289; 276-290; 277-291; 278-292; 279-293; 280-294;281-295; 282-296; 283-297; 284-298; 285-299; 286-300; 287-301; 288-302; 289-303; 290-304; 291-305; 292-306; 293-307; 294-308; 295-309; 296-310; 297-311; 298-312; 299-313; 300-314; 301-315; 302-316; 303-317; 304-318; 305-319; 306-320; 307-321; 308-322; 309-323; 310-324; 311-325; 312-326; 313-327; 314-328; 315-329; 316-330; 317-331; 318-332; 319-333; 320-334; 321-335; 322-336; 323-337; 324-338; 325-339; 326-340; 327-341; 328-342; 329-343; 330-344; 331-345; 332-346; 333-347; 334-348; 335-349; 336-350; 337-351; 338-352; 339-353; 340-354; 341-355; 342-356; 343-357; 344-358; 345-359; 346-360; 347-361; 348-362; 349-363; 350-364; 351-365; 352-366; 353-367; 354-368; 355-369; 356-370; 357-371; 358-372; 359-373; 360-374; 361-375; 362-376; 363-377; 364-378; 365-379; 366-380; 367-381; 368-382; 369-383; 370-384; 371-385; 372-386; 373-387; 374-388; 375-389; 376-390; 377-391; 378-392; 379-393; 380-394; 381-395; 382-396; 383-397; 384-398; 385-399; 386-400; 387-401; 388-402; 389-403; 390-404; 391-405; 392-406; 393-407; 394-408; 395-409; 396-410; 397-411; 398-412; 399-413; 400-414; 401-415; 402-416; 403-417; 404-418; 405-419; 406-420; 407-421; 408-422; 409-423; 410-424; 411-425; 412-426; 413-427; 414-428; 415-429; 416-430; 417-431; 418-432; 419-433; 420-434; 421-435; 422-436; 423-437; 424-438; 425-439; 426-440; 427-441; and 428-442;

wherein the immunogenic fragment, when administered to a subject in a suitable composition which can include an adjuvant, or a suitable carrier coupled to the polypeptide, is capable of raising an immune response that recognizes a polypeptide having the sequence of SEQ ID NOs: 2, 4, 6 or 8.

APPENDIX A1: PENDING CLAIMS (CLEAN COPY) – (continued)

61. The isolated polypeptide of Claim 60 wherein the isolated polypeptide comprises the amino acid sequence of SEQ ID NOs:2, 4, 6 or 8.

62. The isolated polypeptide of claim 61 wherein the isolated polypeptide consists of the amino acid sequence of SEQ ID NOs:2, 4, 6 or 8.

63. A fusion protein comprising the isolated polypeptide of Claim 60 and a polypeptide selected to provide T helper epitopes or assist in recombinant expression.

64. An immunogenic composition comprising the polypeptide of Claim 60 and a pharmaceutically acceptable carrier.

65. The immunogenic composition of Claim 55, wherein the composition comprises at least one other *Neisseria meningitidis* antigen.

66. The isolated polypeptide of claim 60, wherein the immunogenic fragment is selected from the following contiguous segments:
1-15; 2-16; 3-17; 4-18; 5-19; 6-20; 7-21; 8-22; 9-23; 10-24; 11-25; 12-26; 13-27; 14-28; 15-29; 16-30; 17-31; 18-32; 19-33; 20-34; 21-35; 22-36; 23-37; 24-38; 25-39; 26-40; 27-41; 28-42; 29-43; 30-44; 31-45; 32-46; 33-47; 34-48; 45-49; 46-50; 37-51; 38-52; 39-53; 40-54; 41-55; 42-56; 43-57; 44-58; 45-59; 46-60; 47-61; 48-62; 49-63; 50-64; 51-65; 52-66; 53-67; 54-68; 55-69; 56-70; 57-71; 58-72; 59-73; 60-74; 61-75; 62-76; 63-77; 64-78; 65-79; 66-80; 67-81; 68-82; 69-83; 70-84; 71-85; 72-86; 73-87; 74-88; 75-89; 76-90; 77-91; 78-92; 79-93; 80-94; 81-95; 82-96; 83-97; 84-98; 85-99; 86-100; 87-101; 88-102; 89-103; 90-104; 91-105; 92-106; 93-107; 94-108; 95-109; 96-110; 97-111; 98-112; 99-113; 100-114; 101-115; 102-116; 103-117; 104-118; 105-119;

APPENDIX A1: PENDING CLAIMS (CLEAN COPY) – (continued)

106-120; 107-121; 108-122; 109-123; 110-124; 111-125; 112-126; 113-127; 114-128; 115-129; 116-130; 117-131; 118-132; 119-133; 120-134; 121-135; 122-136; 123-137; 124-138; 125-139; 126-140; 127-141; 128-142; 129-143; 130-144; 131-145; 132-146; 133-147; 134-148; 135-149; 136-150; 137-151; 138-152; 139-153; 140-154; 141-155; 142-156; 143-157; 144-158; 145-159; 146-160; 147-161; 148-162; 149-163; 150-164; 151-165; 152-166; 153-167; 154-168; 155-169; 156-170; 157-171; 158-172; 159-173; 160-174; 161-175; 162-176; 163-177; 164-178; 165-179; 166-180; 167-181; 168-182; 169-183; 170-184; 171-185; 172-186; 173-187; 174-188; 175-189; 176-190; 177-191; 178-192; 179-193; 180-194; 181-195; 182-196; 183-197; 184-198; 185-199; 186-200; 187-201; 188-202; 189-203; 190-204; 191-205; 192-206; 193-207; 194-208; 195-209; 196-210; 197-211; 198-212; 199-213; 200-214; 201-215; 202-216; 203-217; 204-218; 205-219; 206-220; 207-221; 208-222; 209-223; 210-224; 211-225; 212-226; 213-227; 214-228; 215-229; 216-230; 217-231; 218-232; 219-233; 220-234; 221-235; 222-236; 223-237; 224-238; 225-239; 226-240; 227-241; 228-242; 229-243; 230-244; 231-245; 232-246; 233-247; 234-248; 235-249; 236-250; 237-251; 238-252; 239-253; 240-254; 241-255; 242-256; 243-257; 244-258; 245-259; 246-260; 247-261; 248-262; 249-263; 240-264; 251-265; 252-266; 253-267; 254-268; 255-269; 256-270; 257-271; 258-272; 259-273; 260-274; 261-275; 262-276; 263-277; 264-278; 265-279; 266-280; 267-281; 268-282; 269-283; 270-284; 271-285; 272-286; 273-287; 274-288; 275-289; 276-290; 277-291; 278-292; 279-293; 280-294; 281-295; 282-296; 283-297; 284-298; 285-299; 286-300; 287-301; 288-302; 289-303; 290-304; 291-305; 292-306; 293-307; 294-308; 295-309; 296-310; 297-311; 298-312; 299-313; 300-314; 301-315; 302-316; 303-317; 304-318; 305-319; 306-320; 307-321; 308-322; 309-323; 310-324; 311-325; 312-326; 313-327; 314-328; 315-329; 316-330; 317-331; 318-332; 319-333; 320-334; 321-335; 322-336; 323-337; 324-338; 325-339; 326-340; 327-341; 328-342; 329-343; 330-344; 331-345; 332-346; 333-347; 334-348; 335-349; 336-350; 337-351; 338-352; 339-353; 340-354; 341-355; 342-356; 343-357; 344-358; 345-359; 346-360; 347-361; 348-362; 349-363; 350-364; 351-365; 352-366; 353-367; 354-368; 355-369; 356-370; 357-371; 358-372; 359-373; 360-374; 361-375; 362-376; 363-377; 364-378; 365-379;

APPENDIX A1: PENDING CLAIMS (CLEAN COPY) – (continued)

366-380; 367-381; 368-382; 369-383; 370-384; 371-385; 372-386; 373-387; 374-388; 375-389; 376-390; 377-391; 378-392; 379-393; 380-394; 381-395; 382-396; 383-397; 384-398; 385-399; 386-400; 387-401; 388-402; 389-403; 390-404; 391-405; 392-406; 393-407; 394-408; 395-409; 396-410; 397-411; 398-412; 399-413; 400-414; 401-415; 402-416; 403-417; 404-418; 405-419; 406-420; 407-421; 408-422; 409-423; 410-424; 411-425; 412-426; 413-427; 414-428; 415-429; 416-430; 417-431; 418-432; 419-433; 420-434; 421-435; 422-436; 423-437; 424-438; 425-439; 426-440; 427-441; and 428-442.

67. An immunogenic composition comprising the polypeptide of Claim 66 and a pharmaceutically acceptable carrier.

68. The immunogenic composition of Claim 67, wherein the composition comprises at least one other *Neisseria meningitidis* antigen.

69. A fusion protein comprising the isolated polypeptide of claim 66.

70. The isolated polypeptide of claim 60, wherein the immunogenic fragment is selected from the following contiguous segments:
1-15; 2-16; 3-17; 4-18; 5-19; 6-20; 7-21; 8-22; 9-23; 10-24;11-25; 12-26; 13-27; 14-28; 15-29; 16-30; 17-31; 18-32; 19-33; 20-34; 21-35; 22-36; 23-37; 24-38; 25-39; 26-40; 27-41; 28-42; 29-43; 30-44; 31-45; 32-46; 33-47; 34-48; 45-49; 46-50; 37-51; 38-52; 39-53; 40-54; 41-55; 42-56; 43-57; 44-58; 45-59; 46-60; 47-61; 48-62; 49-63; 50-64; 51-65; 52-66; 53-67; 54-68; 55-69; 56-70; 57-71; 58-72; 59-73; 60-74; 61-75; 62-76; 63-77; 64-78; 65-79; 66-80; 67-81; 68-82; 69-83; 70-84; 71-85; 72-86; 73-87; 74-88; 75-89; 76-90; 77-91; 78-92; 79-93; 80-94; 81-95; 82-96; 83-97; 84-98; 85-99; 86-100; 87-101; 88-102; 89-103; 90-104; 91-105; 92-106; 93-107; 94-108; 95-109; 96-110; 97-111; 98-112; 99-113; 100-114;101-115; 102-116; 103-117; 104-118; 105-119;

APPENDIX A1: PENDING CLAIMS (CLEAN COPY) – (continued)

106-120; 107-121; 108-122; 109-123; 110-124;111-125; 112-126; 113-127; 114-128; 115-129; 116-130; 117-131; 118-132; 119-133; 120-134;121-135; 122-136; 123-137; 124-138; 125-139; 126-140; 127-141; 128-142; 129-143; 130-144; 131-145; 132-146; 133-147; 134-148; 135-149; 136-150; 137-151; 138-152; 139-153; 140-154; 141-155; 142-156; 143-157; 144-158; 145-159; 146-160; 147-161; 148-162; 149-163; 150-164; 151-165; 152-166; 153-167; 154-168; 155-169; 156-170; 157-171; 158-172; 159-173; 160-174; 161-175; 162-176; 163-177; 164-178; 165-179; 166-180; 167-181; 168-182; 169-183; 170-184; 171-185; 172-186; 173-187; 174-188; 175-189; 176-190; 177-191; 178-192; 179-193; 180-194; 181-195; 182-196; 183-197; 184-198; 185-199; 186-200; 187-201; 188-202; 189-203; 190-204; 191-205; 192-206; 193-207; 194-208; 195-209; 196-210; 197-211; 198-212; 199-213; 200-214; 201-215; 202-216; 203-217; 204-218; 205-219; 206-220; 207-221; 208-222; 209-223; 210-224; 211-225; 212-226; 213-227; 214-228; 215-229; 216-230; 217-231; 218-232; 219-233; 220-234; 221-235; 222-236; 223-237; 224-238; 225-239; 226-240; 227-241; 228-242; 229-243; 230-244; 231-245; 232-246; 233-247; 234-248; 235-249; 236-250; 237-251; 238-252; 239-253; 240-254; 241-255; 242-256; 243-257; 244-258; 245-259; 246-260; 247-261; 248-262; 249-263; 240-264; 251-265; 252-266; 253-267; 254-268; 255-269; 256-270; 257-271; 258-272; 259-273; 260-274; 261-275; 262-276; 263-277; 264-278; 265-279; 266-280; 267-281; 268-282; 269-283; 270-284; 271-285; 272-286; 273-287; 274-288; 275-289; 276-290; 277-291; 278-292; 279-293; 280-294; 281-295; 282-296; 283-297; 284-298; 285-299; 286-300; 287-301; 288-302; 289-303; 290-304; 291-305; 292-306; 293-307; 294-308; 295-309; 296-310; 297-311; 298-312; 299-313; 300-314; 301-315; 302-316; 303-317; 304-318; 305-319; 306-320; 307-321; 308-322; 309-323; 310-324; 311-325; 312-326; 313-327; 314-328; 315-329; 316-330; 317-331; 318-332; 319-333; 320-334; 321-335; 322-336; 323-337; 324-338; 325-339; 326-340; 327-341; 328-342; 329-343; 330-344; 331-345; 332-346; 333-347; 334-348; 335-349; 336-350; 337-351; 338-352; 339-353; 340-354; 341-355; 342-356; 343-357; 344-358; 345-359; 346-360; 347-361; 348-362; 349-363; 350-364; 351-365; 352-366; 353-367; 354-368; 355-369; 356-370; 357-371; 358-372; 359-373; 360-374; 361-375; 362-376; 363-377; 364-378; 365-379;

366-380; 367-381; 368-382; 369-383; 370-384; 371-385; 372-386; 373-387; 374-388; 375-389; 376-390; 377-391; 378-392; 379-393; 380-394; 381-395; 382-396; 383-397; 384-398; 385-399; 386-400; 387-401; 388-402; 389-403; 390-404; 391-405; 392-406; 393-407; 394-408; 395-409; 396-410; 397-411; 398-412; 399-413; 400-414; 401-415; 402-416; 403-417; 404-418; 405-419; 406-420; 407-421; 408-422; 409-423; 410-424; 411-425; 412-426; 413-427; 414-428; 415-429; 416-430; 417-431; 418-432; 419-433; 420-434; 421-435; 422-436; 423-437; 424-438; 425-439; 426-440; 427-441; and 428-442.

71. An immunogenic composition comprising the polypeptide of Claim 66 and a pharmaceutically acceptable carrier.

72. The immunogenic composition of Claim 67, wherein the composition comprises at least one other *Neisseria meningitidis* antigen.

73. A fusion protein comprising the isolated polypeptide of claim 66.

74. The isolated polypeptide of claim 60, wherein the immunogenic fragment is selected from the following contiguous segments:
1-15; 2-16; 3-17; 4-18; 5-19; 6-20; 7-21; 8-22; 9-23; 10-24; 11-25; 12-26; 13-27; 14-28; 15-29; 16-30; 17-31; 18-32; 19-33; 20-34; 21-35; 22-36; 23-37; 24-38; 25-39; 26-40; 27-41; 28-42; 29-43; 30-44; 31-45; 32-46; 33-47; 34-48; 45-49; 46-50; 37-51; 38-52; 39-53; 40-54; 41-55; 42-56; 43-57; 44-58; 45-59; 46-60; 47-61; 48-62; 49-63; 50-64; 51-65; 52-66; 53-67; 54-68; 55-69; 56-70; 57-71; 58-72; 59-73; 60-74; 61-75; 62-76; 63-77; 64-78; 65-79; 66-80; 67-81; 68-82; 69-83; 70-84; 71-85; 72-86; 73-87; 74-88; 75-89; 76-90; 77-91; 78-92; 79-93; 80-94; 95-109; 96-110; 97-111; 98-112; 99-113; 100-114; 101-115; 102-116; 103-117; 104-118; 105-119; 106-120; 107-121; 108-122; 109-123; 110-124; 111-125; 112-126; 113-127; 114-128; 115-129; 116-130; 117-

APPENDIX A1: PENDING CLAIMS (CLEAN COPY) – (continued)

131; 118-132; 119-133; 120-134; 121-135; 122-136; 123-137; 124-138; 125-139; 126-140; 127-141; 128-142; 129-143; 130-144; 131-145; 132-146; 133-147; 134-148; 135-149; 136-150; 137-151; 138-152; 139-153; 140-154; 141-155; 142-156; 143-157; 144-158; 145-159; 146-160; 147-161; 148-162; 149-163; 150-164; 151-165; 152-166; 153-167; 154-168; 155-169; 156-170; 157-171; 158-172; 159-173; 160-174; 161-175; 162-176; 163-177; 164-178; 165-179; 166-180; 167-181; 168-182; 169-183; 170-184; 171-185; 172-186; 173-187; 174-188; 175-189; 176-190; 177-191; 178-192; 179-193; 180-194; 181-195; 182-196; 183-197; 184-198; 185-199; 186-200; 187-201; 188-202; 189-203; 190-204; 191-205; 192-206; 193-207; 194-208; 195-209; 196-210; 197-211; 198-212; 199-213; 200-214; 201-215; 202-216; 203-217; 204-218; 205-219; 206-220; 207-221; 208-222; 209-223; 210-224; 211-225; 212-226; 213-227; 214-228; 215-229; 216-230; 217-231; 218-232; 219-233; 220-234; 221-235; 222-236; 223-237; 224-238; 225-239; 226-240; 227-241; 228-242; 229-243; 230-244; 231-245; 232-246; 233-247; 234-248; 235-249; 236-250; 237-251; 238-252; 239-253; 240-254; 241-255; 242-256; 243-257; 244-258; 245-259; 246-260; 247-261; 248-262; 249-263; 240-264; 251-265; 252-266; 253-267; 254-268; 255-269; 256-270; 257-271; 258-272; 259-273; 260-274; 261-275; 262-276; 263-277; 264-278; 265-279; 266-280; 267-281; 268-282; 269-283; 270-284; 271-285; 272-286; 273-287; 274-288; 275-289; 276-290; 277-291; 278-292; 279-293; 280-294; 281-295; 282-296; 283-297; 284-298; 285-299; 286-300; 287-301; 288-302; 289-303; 290-304; 291-305; 292-306; 293-307; 294-308; 295-309; 296-310; 297-311; 298-312; 299-313; 300-314; 301-315; 302-316; 303-317; 304-318; 305-319; 306-320; 307-321; 308-322; 309-323; 310-324; 311-325; 312-326; 313-327; 314-328; 315-329; 316-330; 317-331; 318-332; 319-333; 320-334; 321-335; 322-336; 323-337; 324-338; 325-339; 326-340; 327-341; 328-342; 329-343; 330-344; 331-345; 332-346; 333-347; 334-348; 335-349; 336-350; 337-351; 338-352; 339-353; 340-354; 341-355; 342-356; 343-357; 344-358; 345-359; 346-360; 347-361; 348-362; 349-363; 350-364; 351-365; 352-366; 353-367; 354-368; 355-369; 356-370; 357-371; 358-372; 359-373; 360-374; 361-375; 362-376; 363-377; 364-378; 365-379; 366-380; 367-381; 368-382; 369-383; 370-384; 371-385; 372-386; 373-387; 374-388; 375-389; 376-390; 377-

APPENDIX A1: PENDING CLAIMS (CLEAN COPY) – (continued)

391; 378-392; 379-393; 380-394; 381-395; 382-396; 383-397; 384-398; 385-399; 386-400; 387-401; 388-402; 389-403; 390-404; 391-405; 392-406; 393-407; 394-408; 395-409; 396-410; 397-411; 398-412; 399-413; 400-414; 401-415; 402-416; 403-417; 404-418; 405-419; 406-420; 407-421; 408-422; 409-423; 410-424; 411-425; 412-426; 413-427; 414-428; 415-429; 416-430; 417-431; 418-432; 419-433; 420-434; 421-435; 422-436; 423-437; 424-438; 425-439; 426-440; 427-441; and 428-442.

75. The isolated polypeptide of claim 60, wherein the immunogenic fragment is selected from the following contiguous segments:
1-15; 2-16; 3-17; 4-18; 5-19; 6-20; 7-21; 8-22; 9-23; 10-24;11-25; 12-26; 13-27; 14-28; 15-29; 16-30; 17-31; 18-32; 19-33; 20-34;21-35; 22-36; 23-37; 24-38; 25-39; 26-40; 27-41; 28-42; 29-43; 30-44;31-45; 32-46; 33-47; 34-48; 45-49; 46-50; 37-51; 38-52; 39-53; 40-54;41-55; 42-56; 43-57; 44-58; 45-59; 46-60; 47-61; 48-62; 49-63; 50-64;51-65; 52-66; 53-67; 54-68; 55-69; 56-70; 57-71; 58-72; 59-73; 60-74;61-75; 62-76; 63-77; 64-78; 65-79; 66-80; 67-81; 68-82; 69-83; 70-84;71-85; 72-86; 73-87; 74-88; 75-89; 76-90; 77-91; 78-92; 79-93; 80-94; 81-95; 82-96; 83-97; 84-98; 85-99; 86-100; 87-101; 88-102; 89-103; 90-104; 91-105; 92-106; 93-107; 94-108; 95-109; 96-110; 97-111; 98-112; 99-113; 100-114;101-115; 102-116; 103-117; 104-118; 105-119; 106-120; 107-121; 108-122; 109-123; 110-124;111-125; 112-126; 113-127; 114-128; 115-129; 116-130; 117-131; 118-132; 119-133; 120-134;121-135; 122-136; 123-137; 124-138; 125-139; 126-140; 127-141; 128-142; 129-143; 130-144;131-145; 132-146; 133-147; 134-148; 135-149; 136-150; 137-151; 138-152; 139-153; 140-154;141-155; 142-156; 143-157; 144-158; 145-159; 146-160; 147-161; 148-162; 149-163; 150-164;151-165; 152-166; 153-167; 154-168; 155-169; 156-170; 157-171; 158-172; 159-173; 160-174;161-175; 162-176; 163-177; 164-178; 165-179; 166-180; 167-181; 168-182; 169-183; 170-184;171-185; 172-186; 173-187; 174-188; 175-189; 176-190; 177-191; 178-192; 179-193; 180-194;181-195; 182-196; 183-197; 184-198; 185-199; 186-200; 187-201; 188-202; 189-203; 190-204;191-205; 192-206; 193-207; 194-208; 195-209;

APPENDIX A1: PENDING CLAIMS (CLEAN COPY) – (continued)

196-210; 197-211; 198-212; 199-213; 200-214;201-215; 202-216; 203-217; 204-218; 205-219; 206-220; 207-221; 208-222; 209-223; 210-224;211-225; 212-226; 213-227; 214-228; 215-229; 216-230; 217-231; 218-232; 219-233; 220-234;221-235; 222-236; 223-237; 224-238; 225-239; 226-240; 227-241; 228-242; 229-243; 230-244;231-245; 232-246; 233-247; 234-248; 235-249; 236-250; 237-251; 238-252; 239-253; 240-254; 241-255; 242-256; 243-257; 244-258; 245-259; 246-260; 247-261; 248-262; 249-263; 240-264; 251-265; 252-266; 253-267; 254-268; 255-269; 256-270; 257-271; 258-272; 259-273; 260-274; 261-275; 262-276; 263-277; 264-278; 265-279; 266-280; 267-281; 268-282; 269-283; 270-284; 271-285; 272-286; 273-287; 274-288; 275-289; 276-290; 277-291; 278-292; 279-293; 280-294; 281-295; 282-296; 283-297; 284-298; 285-299; 286-300; 287-301; 288-302; 289-303; 290-304; 291-305; 292-306; 293-307; 294-308; 295-309; 296-310; 297-311; 298-312; 299-313; 300-314; 301-315; 302-316; 303-317; 304-318; 305-319; 306-320; 307-321; 308-322; 309-323; 310-324; 311-325; 312-326; 313-327; 314-328; 315-329; 316-330; 317-331; 318-332; 319-333; 320-334; 321-335; 322-336; 323-337; 324-338; 325-339; 326-340; 327-341; 328-342; 329-343; 330-344; 331-345; 332-346; 333-347; 334-348; 335-349; 336-350; 337-351; 338-352; 339-353; 340-354; 341-355; 342-356; 343-357; 344-358; 345-359; 346-360; 347-361; 348-362; 349-363; 350-364; 351-365; 352-366; 353-367; 354-368; 355-369; 356-370; 357-371; 358-372; 359-373; 360-374; 361-375; 362-376; 363-377; 364-378; 365-379; 366-380; 367-381; 368-382; 369-383; 370-384; 371-385; 372-386; 373-387; 374-388; 375-389; 376-390; 377-391; 378-392; 379-393; 380-394; 381-395; 382-396; 383-397; 384-398; 385-399; 386-400; 387-401; 388-402; 389-403; 390-404; 391-405; 392-406; 393-407; 394-408; 395-409; 396-410; 397-411; 398-412; 399-413; 400-414; 401-415; 402-416; 403-417; 404-418; 405-419; 406-420; 407-421; 408-422; 409-423; 410-424; 411-425; 412-426; 413-427; 414-428; 415-429; 416-430; 417-431; 418-432; 419-433; 420-434; 421-435; 422-436; 423-437; 424-438; 425-439; 426-440; 427-441; and 428-442.

APPENDIX A1: PENDING CLAIMS (CLEAN COPY) – (continued)

76. An immunogenic composition comprising the polypeptide of Claim 75 and a pharmaceutically acceptable carrier.

77. The immunogenic composition of Claim 76, wherein the composition comprises at least one other *Neisseria meningitidis* antigen.

78. A fusion protein comprising the isolated polypeptide of claim 75.

Appendix B

BLAST 2 SEQUENCES

This tool produces the alignment of two given sequences using BLAST engine for local alignment. The stand-alone executable for blasting two sequences (bl2seq) can be retrieved from NCBI ftp site
Reference: Tatiana A. Tatusova, Thomas L. Madden (1999), "Blast 2 sequences - a new tool for comparing protein and nucleotide sequences", FEMS Microbiol Lett. 174:247-250

Program blastp Matrix Not Applicable

Parameters used in BLASTN program only:
Reward for a match: **Penalty for a mismatch:**

Open gap 11 and extension gap 1 penalties
gap x_dropoff 50 expect 10 word size 3 Filter

Sequence 1 Enter accession or GI or download from file
Browse...
or sequence in FASTA format from: to:

```
MKVSLSTLTLSILSCFAILAIQQAQAVPNPVAFVDEVRSENDLGQDNELPIDVQSATQSA
STDTANPLDEHEPELYTTAL
ENKTMLINCSALNQDIMRLACYDTLVHGETPAVIKTKRSIRLDETIWQTIKGKPQVIYQE
TTDPIFLMGNEKGMLTKKDA
KQLEYAAKQFTPLSLSFDLDRNNTPLWSSRPHNPMYVLPIFMHGKPNRSPNTPSHEAKQF
TPNEFRAPELKFQVSVKVKAAEDLWGTDSDLWFGYTQQSHWQIFNGKNSRPFRVHDYQPE
IFLTQPVYSDLPWDGKVRMIGMGAVHHPNGESAKLERSWNRAYLMAGMEWKNLTVMPRIW
```

Sequence 2 Enter accession or GI or download from file
Browse...
or sequence in FASTA format from: to:

```
MKFNKIALAVIAAVAAPVAAPVAAQAGVTVSPLLLGYHYTDEAHNDQRKILRTGKKLELD
ATNAPAPANGGVALDSELWTGAAIGIELTPSTQFQVEYGISNRDAKSSDKSAHRFDAEQE
TISGNFLIGTEQFSGYNPTNKFKPYVLVGAGQSKIKVNAIDGYTAEVANGIAKDQAVKAG
QEVAESKDTIGNLGLGARYLVNDALALRGEARAIHNFDNKWWEGLALAGLEVTLGGRLAV
PVAPVAEPVAEPVVAPAPVILPKPEPEPVIEEAPAVIEDIVVDSDGDGVPDHLDACPGTP
VNTVVDPRGCPVQVNLVEELRQELRVFFDYDKSIIKPQYREEVAKVAAQMREFPNATATI
SEARANAVKSMLSNEFGIAPNRLNAVGYGFDRPIAPNTTAE
```

Align Clear Input

SEQ ID NO: 2 of 09/787,083

SAHAR et Al Sequence

Comments and suggetstions to: blast-help@ncbi.nlm.nih.gov
Credits to: Tatiana Tatusov and Tom Madden

C

NCBI Blast 2 Sequences results

BLAST 2 SEQUENCES RESULTS VERSION BLASTP 2.1.2 [Oct-19-2000]

Matrix BLOSUM62 gap open: 11 gap extension: 1
x_dropoff: 50 expect: 10.00 wordsize: 3 Filter Align

Sequence 1 lcl|seq_1 **Length** 442 (SEQ ID NO:2 of 09/787,083)
Sequence 2 lcl|seq_2 **Length** 449 (Sarwar et al)
No significant similarity was found